

Amendment to the Claims:

1.-21. (Cancelled)

22. (Currently amended) A method of screening for substances which ~~are capable of~~ inhibiting the phosphorylation of a tau protein by casein kinase 1 (CK1), wherein the tau protein comprises one or more phosphorylation sites, the method comprising:

(a) ~~exposing contacting~~ at least one candidate substance, the tau protein of SEQ ID NO: 2 or a tau variant having at least 95% sequence identity with SEQ ID NO: 2 and casein kinase 1 of SEQ ID NO: 1, or a CK1 variant having greater at least 95% identity with SEQ ID NO: 1 under ~~to~~ conditions under which said ~~in which~~ the casein kinase 1 or variant thereof phosphorylates said tau protein or variant thereof at one or more sites selected from the group consisting of (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435, is capable of phosphorylating the site(s) of the tau protein in the absence of the candidate substance said casein kinase 1 having greater than 80% sequence identity with full length casein kinase 1 that has the amino acid sequence set out between amino acids 1 and 428 inclusive of SEQ ID NO: 1, and said tau protein having greater than 80% sequence identity with full length tau protein that has the amino acid sequence set out between amino acids 1 and 441 inclusive of SEQ ID NO: 2;

(b) determining whether, and optionally the extent to which, the candidate substance inhibits said ~~phosphorylation~~ phosphorylating of the tau protein, by identifying the site(s) at which the casein kinase 1 phosphorylates the tau protein, said site(s) being at least one selected from the group consisting of (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435 of tau protein; and

(c) selecting the candidate substance which inhibits phosphorylation of the tau protein ~~or variant~~ at one or more of the sites.

23. (Currently amended) The method of claim 22, wherein the casein kinase 1 is a fragment or derivative of full length casein kinase 1 ~~having which is at least 95% identical to the amino-~~

~~acid sequence set out between amino acids 1 and 428 inclusive in SEQ ID NO: 1.~~

24-25. (Cancelled)

26. (Previously presented) The method of claim 22, wherein the tau protein is paired helical filament tau.

27. (Currently Amended) The method of claim 22, wherein the tau protein is a fragment or derivative ~~which is at least 95% identical with~~ of full length tau protein having the amino acid sequence set out between amino acids 1 and 441 inclusive in SEQ ID NO: 2.

28.-30. (Cancelled)

31. (Withdrawn) The method of claim 22, wherein the sites of the tau protein are selected from S262 and/or S356.

32. (Previously presented) The method of claim 22, wherein the sites of the tau protein are one or more sites selected from the group consisting of S113, S258, S289, S416, S433 and S435.

33. (Withdrawn) The method of claim 22, wherein the method comprises determining the effect of contacting the candidate substance(s) with a combination of kinases, simultaneously or sequentially applied to the candidate substances and casein kinase 1.

34. (Withdrawn) The method of claim 33, wherein the combination of kinases comprises casein kinase 1 (CK1) in combination with one or more of casein kinase 2 (CK2), protein kinase A (PKA), glycogen synthase kinase 3 α (GSK-3 α) or glycogen synthase kinase 3 β (GSK-3 β).

35. (Withdrawn) The method of claim 33, wherein the combination of kinases comprises casein kinase 1 (CK1) in combination with PKA and GSK-3 β .

36. (Previously presented) The method of claim 22, wherein the method further comprises

determining in step (b) whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of another substrate by the casein kinase 1.

37. (Cancelled)

38. (Previously presented) The method of claim 36, wherein the method further comprises confirming whether a candidate substance selected in an initial screen has the property of inhibiting the phosphorylation of the tau protein under conditions in which the casein kinase 1 is capable of phosphorylating the site(s) of the tau protein in the absence of the candidate substance.

39. (Previously presented) The method of claim 22, wherein the step of determining the presence, absence or extent of phosphorylation at one or more sites of the tau protein employs mass spectroscopy or a site specific recognition agent which is capable of distinguishing between a phosphorylated and a non-phosphorylated site.

40. (Withdrawn) The method of claim 39, wherein the site specific recognition agent is a monoclonal antibody.

41. (Previously presented) The method of claim 22, wherein the screening is carried out in a multiplex assay employing a solid phase on which a plurality of substrates are immobilised.

42. (Original) The method of claim 41, wherein the substrates correspond to phosphorylation sites of tau protein.

43. (Withdrawn) The method of claim 22, comprising the further step of optimising the structure of the selected candidate substance.

44. (Withdrawn) The method of claim 22 which comprises at least one of the further steps of manufacturing the selected candidate substance and formulating the selected candidate substance in a pharmaceutical composition.

45. (Withdrawn) A method of preparing a pharmaceutical composition or medicament, the method comprising:

(i) identifying a casein kinase 1 inhibitor according to claim 22;

(ii) optimising the structure of the casein kinase 1 inhibitor; and

(iii) preparing the pharmaceutical composition or medicament containing the optimised casein kinase 1 inhibitor.

46. (Withdrawn) A substance obtained by the method of claim 22.

47.– 52. (Cancelled)

53. (Withdrawn) A method for the treatment of a tauopathy in a patient in need of said treatment, said method comprising administering to said patient a substance obtainable by the method of claim 22.

54. (Withdrawn) The method of claim 53 wherein the tauopathy is Alzheimer's disease, frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy (PSP), Pick's disease, corticobasal degeneration, multisystem atrophy (MSA), neurobasal degeneration with iron accumulation, type 1 (Hallervorden-Spatz), argyrophilic grain dementia, Down's syndrome, diffuse neurofibrillary tangles with calcification, dementia pugilistica, Gerstmann-Sträussler-Scheinker disease, myotonic dystrophy, Niemann-Pick disease type C, progressive subcortical gliosis, prion protein cerebral amyloid angiopathy, tangle only dementia, postencephalitic parkinsonism, subacute sclerosing panencephalitis, Creutzfeldt-Jakob disease, amyotrophic lateral sclerosis/parkinsonism-dementia complex, non-Guamanian motor neuron disease with neurofibrillary tangles/dementia, and Parkinson's disease.

55. (Currently amended) The method of claim 22, said phosphorylation site(s) being at least one selected from the group consisting of S113, S237, S238, S258, S289, S412, S413, T414, S416, S433, and S435.